A practical definition of conduction block in Ivlg responsive multifocal motor neuropathy

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Background: Multifocal motor neuropathy with conduction block (MMN) can be mistaken for motor neurone disease or other lower motor neurone syndromes, but is treatable with intravenous immunoglobulin (Ivlg). Formal electrophysiological criteria for conduction block (CB) are so stringent that substantial numbers of patients may miss out on appropriate treatment.

Methods: Electrophysiological data were collected from 10 healthy volunteers and compared to data from 10 patients who satisfied the clinical criteria for MMN and who responded to Ivlg. This produced a definition of CB in MMN patients which was compared with existing definitions to assess "miss rates".

Results: Mean values for compound muscle action potential area, amplitude, and duration were calculated in normal subjects. Results beyond 3 SD of their respective means were considered abnormal. Using these criteria, CB in the context of MMN was defined as a reduction in negative peak area >23% along a distal nerve segment or >29% across a proximal segment; or a reduction in amplitude >32% across a distal segment or >33% across a proximal segment. All Ivlg responsive patients had at least one nerve segment showing such CB. Employing some criteria from the literature would have denied treatment to over 30% of responsive patients.

Conclusion: In the clinical setting of suspected MMN, less stringent criteria for CB can improve the diagnosis of this treatable disorder. Exclusions on grounds of temporal dispersion may be over-restrictive. A little over one third of CBs occur proximally.

Multifocal motor neuropathy (MMN) is an uncommon disorder characterised by slowly progressive asymmetrical lower motor neurone weakness usually starting in the arms with minimal or no sensory symptoms.^{1–3} Relative lack of wasting even in severely weakened muscles is a distinctive early clinical feature.⁴ MMN can be successfully treated with intravenous immunoglobulin (Ivlg).^{5–11} It is crucial to distinguish this treatable condition from other motor neurone diseases.

The electrophysiological hallmark of MMN is conduction block (CB), in which an action potential fails to propagate through a segment of an intact axon. Various working definitions of CB have been proposed.^{10–12–21} The presence of any temporal dispersion (TD) has been seen as a major obstacle to satisfactory definition of CB. Many of the existing definitions of CB either do not accommodate TD or demand even more stringent criteria in its presence. This could reduce sensitivity for electrophysiological detection of this potentially treatable disorder. Tighter criteria for defining CB demand more protracted neurophysiological assessment, which may be impractical in many healthcare settings. We have explored less stringent definitions of CB in patients with MMN, with a view to increasing sensitivity for identifying Ivlg responsive patients.

METHODS

Sensory and motor neurophysiological examinations were performed in 10 healthy controls using standardised techniques. The mean age in this group was 40.3 (range 31–58) years. Distal sensory responses were assessed in the median and ulnar nerves, measuring peak-to-peak amplitudes and conduction velocities. Motor stimulation of peripheral nerves at the wrist, elbow, axilla, and Erb's point was performed at standard sites with a Devices Type 3072 stimulator (Digitimer, Welwyn Garden City, Herts, UK) and a conventional bipolar stimulating electrode. Stimulation of

the C8 root was performed using a Devices Type 180 stimulator (Digitimer) and saline soaked lint covered with silver electrodes (each electrode area 1 cm²) with the cathode positioned in the space between the spinous processes of the C7 and T1 vertebrae.²² Compound muscle action potentials (CMAPs) were recorded using standard AgCl electrodes and a Medelec Mystro instrument (Medelec, Old Woking, Surrey, UK). For the median nerve, CMAPs were recorded from the left and right abductor pollicis brevis following supramaximal stimulation of the nerve at the wrist, elbow, axilla (in one patient), Erb's point, or over the C8 root. For the ulnar nerve, CMAPs were recorded from the left and right abductor digiti minimi following supramaximal stimulation at the wrist, below and above the elbow, the axilla (in one patient), Erb's point, or over the C8 root. Entrapment sites were excluded from assessment of CB. Measurements were made for negative peak amplitudes, negative peak areas, negative peak durations, distal latencies (DL), conduction velocities, and F-waves. For the last three parameters, the American Academy AIDS Task Force criteria were used to calculate prolongations in the "demyelinating range".²³ The percentage reduction in CMAP area and amplitude between two adjacent points of stimulation were calculated using the formula: (dCMAP–pCMAP/dCMAP)×100%, where dCMAP and pCMAP represent distal and proximal CMAP values, respectively. Percentage increase in duration in the proximal segment relative to the distal segment was used to calculate TD using the formula: (pCMAP duration–dCMAP duration/dCMAP duration)×100%. Nerves with distal CMAP amplitudes of <1.0 mV were not accepted for measurement of CB because of the likelihood of errors in measurement.

Abbreviations: CB, conduction block; CMAP, compound muscle action potential; DL, distal latencies; Ivlg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; TD, temporal dispersion

The mean (standard deviation, SD) percentage drops in CMAP amplitudes and areas and increases in duration across the distal (wrist to elbow) and proximal segments (elbow to neck) for healthy controls were calculated (for explanation, see below). We used values in excess of 3 SD of the respective means to define CB and TD.

We then applied these values to detect CB in 10 patients with a clinical diagnosis of MMN who responded to IvIg. All patients had a chronic asymmetric, predominantly distal, lower motor neurone weakness, with disproportionate preservation of muscle bulk and without sensory involvement. A neurologist (MD) with extensive experience in managing peripheral nerve disorders performed the clinical observations while being blinded to the neurophysiological results. Clinical improvement in the IvIg responsive patients was defined as: (i) an improvement in MRC score by at least one grade in one or more affected muscle groups; and (ii) a clear functional improvement in performance of simple activities that had been affected by the patient's weakness. All but one patient remain under follow up at the time of preparing this manuscript, all maintaining their clinical improvement on regular IvIg.

RESULTS

Controls

Data were obtained from 37 nerves and 74 nerve segments in healthy controls. Mean (SD) reductions in amplitude and area and mean TD are shown in table 1.

CMAPs from C8 stimulation were either equal or greater in size compared with those recorded from Erb's point. Therefore, for the assessment of area, amplitude, and duration, the proximal segment was defined as the elbow to neck segment. The same was true for eight IvIg responsive patients. In two other IvIg responsive patients, where only limited studies could be performed, the elbow–Erb's point and elbow–axilla segments were taken as the proximal segments, respectively.

MMN patients

Six of the IvIg responsive patients were males and four were females. The mean (SD) age of onset of symptoms was 44.2 (15.6) years and the mean duration of illness at the start of treatment with IvIg was 10.9 (7.6) years. The upper limb was involved first in six patients, the lower limb in three, and the illness started in both upper and lower limbs in one patient. Finger or wrist drop at or within 1 year of onset was seen in 4/10 patients. Myotonia and/or cramps were present in four patients. Wasting was absent or mild in 5/10 patients, even in severely weakened muscles. Although one patient reported mild sensory symptoms, sensory conduction was normal in all. None of the patients had upper motor neurone signs. Two patients had anti-GM1 antibodies. All three patients who had received steroids previously had worsened with that treatment. The average follow up period so far is 48.3

(25.3) months, ranging from 6 months (in a patient who emigrated shortly afterwards) and 7 years.

Using mean+3 SD values over healthy controls, CB was defined as a reduction in negative peak area >23% in a distal segment and >29% in a proximal segment, or a reduction in amplitude of >32% for a distal segment and >33% for a proximal segment (table 1).

Altogether 72 nerve segments were studied in the IvIg responsive group. Each patient in this group had at least one nerve segment with a reduction in area suggestive of CB. Using the area criteria, one patient had one CB, two patients had two CBs, four patients had three CBs, two patients had four CBs, and another patient had five CBs. Twelve of these 30 segments (40%) were proximal. Eight patients had area reductions in excess of 50% in at least one nerve segment. The largest area reductions in the other two patients were 37% and 40%, both seen in distal segments. Twenty six of the 30 segments where area was reduced also showed a drop in amplitude suggestive of CB. An additional nine segments with amplitude reduction without significant area changes were also present.

TD >37% (table 2) was present in 22 nerve segments. These included 15 segments with concomitant reduction both in area and amplitude, three segments with reduction in amplitude only, and the remaining four segments with no evidence of CB.

In the IvIg responsive group, DL were prolonged into the demyelinating range in two nerves in different patients. Conduction velocities lay in the demyelinating range in one nerve in a separate patient and were found within segments with CB. Out of 36 nerves studied, F-latencies were prolonged into the demyelinating range in one and were absent in 14. Table 2 shows the distal CMAP and TD values in those segments which had CB in our IvIg responsive patients.

Previous criteria for CB

We compared our definition of CB with some of the other definitions available in the literature^{12 14 17 19 21} given that some of the latter criteria may be too stringent for day-to-day diagnosis of MMN. When comparing, we chose the widest and therefore the most inclusive criteria from these papers, when available. This meant that criteria used for "possible CB" rather than "definite CB" were chosen. Applying these criteria to the nerves used in this study, no CB was detected in 20%^{12 14 17} to 30%²¹ of IvIg responsive patients and was missed in up to 57% of the nerves (fig 1).

Proximal segments accounted for 36% (4.8)% of the CBs, with relatively narrow variation between results using different criteria (figs 2 and 3).

DISCUSSION

This study sought a practical electrophysiological definition of CB in patients with MMN who might respond to IvIg therapy. All our patients fulfilled the clinical criteria for MMN and responded to IvIg. Early weakness of finger or wrist extension and a relative lack of wasting in severely weakened muscles, seen in some of our patients, are typical of this disorder.⁴ Three patients had worsened with steroid treatment but subsequently responded to IvIg.⁸ Our clinical and electrophysiological diagnoses of MMN were supported by the sustained improvements that have been maintained at follow up for up to 7 years.

The most useful measure of CB is a proximal reduction in the CMAP area. We found reductions greater than 23% distally and 29% proximally to be predictive of IvIg response. These values were defined from normal controls (mean+3 SD), but even if the highest percentage drop that still distinguishes IvIg responsive MMN patients was taken, the levels could be raised to 37% distally and 50% proximally

Table 1 Changes in CMAP values in healthy controls

Nerve segment	Mean (SD)	Mean+3 SD
Area reductions		
Distal segment	6.3 (5.5)%	23%
Proximal segment	7.5 (7.1)%	29%
Amplitude reductions		
Distal segment	8.5 (7.7)%	32%
Proximal segment	9.2 (8.0)%	33%
Duration increases		
Distal segment	6.8 (9.9)%	37%
Proximal segment	9.8 (8.7)%	36%

Table 2 Distal CMAP amplitudes and TD in segments showing CB in the lvg responsive patients

Patient number	Nerve	Segment	Distal CMAP amplitude (mV)	CB (%)	TD (%)
1	RU	D	4.0	31	22
		P		82	37*
2	LU	D	3.6	68	44*
	LM	D	1.4	52	-7
	LU	P	4.8	49	27
3	RU	P	5.5	40	123*
	LM	D	1.7	40	53*
	RU	D	2.8	39	-15
4	RM	D	12.1	74	29
	LU	P	5.8	78	15
	LM	D	7.3	78	40*
5	RM	D	11	36	23
		P		38	9
		D		53	5
	LM	P	5.5	31	4
		D		27	1
6	RU	D	8.4	32	13
	LU	D	13.4	25	14
	RM	D	10.9	40	7
		P		52	-15
		D		82	72*
7	LU	P	3.2	44	-73
		D		40	128*
		D		71	-15
	RM	P	8.1	70	325*
		D		50	151*
8	LM	P	13.3	44	27
		D		51	76*
		P		36	46*
	LU	D	6.1	46	131*
		D		81	-8
9	RM	P	14.4	45	97*
		D		32	3
		P		53	86*
	LM	P	4.1	29	20
		D		43	105*
10	RU	P	6.5	92	68*
	LU	D	7.0	46	56*

D, distal; L, left; M, median nerve; P, proximal; R, right; U, ulnar nerve.
*Abnormal value.

without altering sensitivity. We also found amplitude reductions greater than 33% proximally or greater than 32% distally to be similarly useful.

Assessment of CB is necessary to differentiate MMN from other lower motor neurone syndromes. In the latter, pseudo-CB may be caused by excessive interphase cancellation in the presence of small distal CMAP amplitudes and often polyphasic waveforms.¹⁴ In our study, we attempted to avoid this by excluding all nerves whose distal CMAP amplitudes were <1.0 mV. TD due to non-uniform conduction is a feature of many chronic demyelinating neuropathies and in such cases interphase cancellation could result in the

mistaken appearance of CB.¹⁴ This situation has led many authors to use TD either as an exclusionary or restrictive criterion for the diagnosis of CB,^{14 15 17 19 21} which although helpful for clinical research, leads to underdiagnosis of treatable patients.^{10 17} Indeed, up to 30% of our patients would have remained electrophysiologically undiagnosed if such criteria had been applied. For instance, patient no. 16 described by Katz *et al*¹⁷ had a typical clinical picture of MMN and a raised anti-GM1 antibody titre. However, her nerve conduction studies showed a 31% drop in median CMAP area across the forearm, which did not constitute CB according to their criteria, but would have according to ours.

Figure 1 Measurement of degree of CB in the forearm median nerve by comparing abductor pollicis brevis CMAP amplitude following stimulation at the wrist (A1) and elbow (A2). Recordings are shown pre-treatment (left) and 2 weeks after 2 g/kg body wt lvg (right).

Figure 2 Number of patients who would show CB in at least one nerve using different diagnostic criteria. Data are from Sumner,¹⁹ Brown and Feasby,¹² Rhee et al,¹⁴ Katz et al,¹⁷ and Taylor et al.²¹

One could argue that more extensive neurophysiological assessment of all limbs could have identified more areas of CB. This is not always practical in routine neurophysiological practice due to time, manpower, and financial constraints. The development of less stringent and more “useable” criteria is, therefore, of practical importance for predicting whether a lower motor neurone disorder will respond to IVIg. Pfeiffer et al²⁴ suggest that “weak” criteria for CB interfere with prediction of response to IVIg. We argue that in the proper clinical context, where the suspicion of MMN is strong, a “weak” criterion is preferable in order to identify *all* responders, even at the cost of undertaking unrewarding treatment trials in a few non-responders. A recent study comparing IVIg responsive versus non-responsive subjects faced the dilemma of having to sacrifice some of sensitivity for more specificity and opted against it.¹⁰ In clinical practice, where the decision lies between diagnosing a treatable condition and an untreatable disorder with potentially grave prognosis, the issue of sensitivity gains priority even at the cost of losing some specificity. The need for less restrictive criteria has been highlighted in other ways. Cappellari et al¹⁸ suggested that the more marked drops in CMAP size may be preceded by smaller decrements which could nevertheless be suggestive of focal pathology in the appropriate clinical context.

TD may be as much an inherent part of MMN as is CB and the two frequently coincide in the same nerve segment.^{24–25} The relations between TD, drop in CMAP amplitude or area, conduction velocity, and DL are complex and may be dependent, among other factors, upon the relative balance between delay and block of axonal conduction among the faster and slower conducting fibres.^{26–27} Preliminary studies suggest that TD improves following IVIg therapy in responsive patients, which improvement may be independent of measurable amplitude or area changes.²⁷

It was of interest that the distribution of CB between proximal and distal segments in our patients remained remarkably similar even when different criteria from the literature were chosen. Proximal segments accounted for mean 36% of the CBs. This is also consistent with a recent study based on MR scans of the brachial plexus,¹⁰ which reported that 12 out of 31 (39%) of the patients who fulfilled the clinical and electrophysiological criteria for MMN had abnormal T2-weighted images of the brachial plexus, sometimes associated with diffuse nerve swelling. In some patients proximal stimulation alone may reveal CB, even when routine electrophysiological tests in the distal segments are normal.²⁸ The importance of testing proximal nerve segments for CB needs particular emphasis.

Figure 3 Number of proximal and distal segments which would show CB using different diagnostic criteria. Data are from Sumner,¹⁹ Brown and Feasby,¹² Taylor et al,²¹ Rhee et al,¹⁴ and Katz et al.¹⁷

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NEUROLOGICAL PICTURE .....

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Delayed recovery of ulnar neuropathy due to elbow warming

A 26 year old student presented clinically with a right ulnar sensory neuropathy, thought to have resulted from compression at the elbow during late night studying. There was no previous history, nor family history, of compression neuropathy; serum glucose and inflammatory markers were not elevated. Nerve conduction studies confirmed marked slowing across the elbow on the right, compared with the left side. Plain x ray of the right elbow revealed no bony abnormality.

Despite resting the arm, hand weakness progressed over the next 6 weeks, with evidence of hand clawing. At this time the student confessed that, in an attempt to stimulate recovery himself, he had fashioned an “elbow warmer” from an electric blanket (fig), which had been worn continuously over the previous weeks. He was instructed not to use it any more, and referred immediately for surgical intervention following which his weakness resolved.

Ulnar neuropathy at the elbow (UNE) remains a controversial entity, both in terms of neurophysiological diagnosis and subsequent management.¹ UNE often improves with conservative management and simple elbow rest, but surgical referral is advised where there is progression of motor symptoms. Although it is not possible to be certain that the use of the “elbow warmer” worsened this patient’s neuropathy, neurophysiology is influenced by temperature.² Heat induced conduction block has been described in the setting of carpal tunnel syndrome,³ and cooling has been successfully used to aid recovery in common peroneal nerve compressive neuropathy.⁴ It is therefore conceivable that this home-made device prevented spontaneous recovery in this patient, necessitating surgical referral.

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Patient consent has been obtained for publication of figure 1

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